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Major Depression, Minor Depression, and Double Depression: Are They Distinct Clinical Entities?

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The clinical concept of "double depression," i.e., the superimposition of a major depressive disorder in a patient with dysthymic disorder, implies that there are at least some differences between dysthymia, major depression, and double depression. However, the relationship between these two syndromes remains unclear. The present study uses genetic methodology to explore any possible relationship between minor depression, double depression, and major depression. From 1988–1990, all consecutive unrelated inpatients and outpatients (index cases) presenting to a university-based mood disorders service had detailed family histories taken, using modification of the "family history method." Diagnoses for index cases and their first-degree relatives were made according to Research Diagnostic Criteria. For all index cases with a diagnosis of minor or intermittent depression, and minor/intermittent depression plus either single or recurrent depression ("double depression"), morbidity risks for mood disorders were calculated for first-degree relatives (parents, siblings, and children) using the maximum likelihood approach. Results showed no significant differences in morbidity risk calculations to first-degree relatives of index cases with minor/intermittent depression, major depression, or double depression. The data from this genetic perspective suggest that single depression, recurrent depression, minor depression, and double depression are indistinguishable.

KEY WORDS: minor depression, double depression, intermittent depression, morbidity risks, major depression

INTRODUCTION

It has only been in recent years that chronic mild depression (minor depression) has been classified in North America as a mood disorder (dysthymic disorder) rather than as an inherited personality trait [Schneider, 1959], intrapsychic/neurotic conflicts [Fenichel, 1945], or complications of other mental/physical disorders or psychosocial stressors [Akiskal and Weise, 1992]. The DSM III-R category of dysthymic disorder is reserved for individuals with chronic (at least 2 years) depressive symptoms that are fewer in number (less than three) than found in DSM III-R major depression (at least five). The DSm III-R category of dysthymia is very similar to the Research Diagnostic Criteria (RDC) categories of minor/intermittent depression (see Table I).

Scientific and clinical debate continues about whether minor depression/dysthymia is a mild form of major depressive disorder or a unique and distinct clinical entity. The clinical concept of "double depression." i.e., the superimposition of a major depressive disorder in a patient with dysthymic disorder, implies that there are at least some differences between these three disorders, i.e., dysthymia, major depression, and double depression [Williams and Spitzer, 1982; Keller and Schapiro, 1982; Keller et al., 1983]. Nevertheless, biological [Howland and Thase, 1991] and treatment intervention [Kocsis et al., 1988; Conte and Karasu, 1992; Howland, 1991; Stewart et al., 1992; Rosenthal et al., 1992] research which has examined this question still provides no unequivocal answer to the relationship between minor and major depression. Genetic methodology provides yet another avenue with which to explore any possible relationship between minor depression, double depression, and major depression.

As part of an ongoing collaboration between the Departments of Medical Genetics and Psychiatry, University of British Columbia, the Mood Disorders Service (MDS) Genetic Database was established and has generated studies on morbidity risk to first-degree rela-

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TABLE I. Major Comparative Components of DSM III-R Dysthymia and RDC Minor and Intermittent Depressive Disorder Diagnoses

	DSM III-R dysthymia	RDC minor depression	RDC intermittent depression
Persistent depressed mood	Yes	Yes	Yes
At least two other depressive symptoms	Yes	Yes	Yes
Minimum duration	2 years	2 weeks	2 years[a]
Major depression may precede disorder	No	?	Yes

[a]With intermittent periods (days/weeks) of normal mood.

tives of index cases with a variety of mood disorders diagnoses (for more details, see Sadovnick et al. [1994]). The present paper focuses on morbidity risks for a mood disorder among first-degree relatives of index cases diagnosed, according to RDC [Spitzer et al., 1977], as having either minor or intermittent depression, or minor or intermittent depression plus single or recurrent ("double") depression. These data are compared with previously published [Sadovnick et al., 1994] morbidity risks for mood disorder among first-degree relatives of index cases with single and recurrent depression.

MATERIALS AND METHODS

The methodology to establish the MDS Genetic Database has been described in detail (total study group, reliability data, diagnostic criteria and categories, demographic data, and comparisons with other genetic studies in the literature) in Sadovnick et al. [1994], and is thus here only reviewed briefly.

Index Cases

During the study period (August, 1988–April, 1990), all consecutive unrelated inpatients and outpatients (index cases) presenting to the MDS had detailed family histories taken by an M.Sc.-level genetic counsellor, who completed additional training for this psychiatric project. Multiple (minimum of two) family informants were interviewed whenever possible. The diagnosis of a mood disorder for the index case was made according to RDC [Sadovnick et al., 1994].

The present study focused on index cases diagnosed with minor/intermittent depression or "double" depression. As stated earlier [Williams and Spitzer, 1982], RDC minor depression and intermittent depression and the DSM III-R dysthymic disorder are very similar (see Table I). This is even more evident in our specific sample, where >60% of index cases with minor/intermittent depression had chronic symptoms (i.e., >2 years' duration), and >80% had symptomatology for >12 months. This is most consistent with the DSM III-R criteria for dysthymic disorder.

Relatives of Index Cases

Although family history information was taken in as much detail as possible, informants were often not sufficiently aware of the presence (or absence) of psychiatric conditions in second- and third-degree relatives. By comparison, information on first-degree relatives was largely reliable in terms of presence or absence of a mood disorder, the availability of at least good descriptive information (and usually permission to obtain psychiatric records), and total number of first-degree relatives used as a reliable denominator. For these reasons, the present study was limited to parents, siblings, and children of index cases.

During the genetic interview, family informants were administered the appropriate Family History RDC questionnaire(s) [Andreason et al., 1977] by the genetic counsellor whenever a relative was reported to have (or to possibly have or have had) a "mood disorder." It is important to note that FHRDC criteria only generate the "generic" diagnoses of depression and/or mania. Specific criteria for minor/intermittent depression and/or hypomania are not operationalized with FHRDC criteria [Andreason et al., 1977].

For each reportedly affected relative, psychiatric records were obtained (with appropriate consent) whenever possible. Data from the FHRDC questionnaire(s) and the psychiatric records (if available) were then reviewed by a psychiatrist (R.A.R.) experienced in the differential diagnosis of mood disorders and a "best-estimate" diagnosis was made, using FHRDC criteria [Sadovnick et al., 1994; Kosten and Rounsaville, 1992].

For the present study, a relative of an index case was considered "affected" with a mood disorder if appropriate available psychiatric records clearly supported the diagnosis according to the criteria, or if sufficient descriptive data were available to clearly fulfill FHRDC criteria, (see Sadvnick et al. [1994] for more details).

Confirmation of the relatives' diagnoses was ensured with intra- and interrate reliability checks (see Sadovnick et al. [1994]). In addition, a subpopulation of relatives was administered the Structured Clinical Interview for DSM III-R (SCID) [Spitzer and Williams, 1985], with near-perfect correlation with the best-estimate FHRDC diagnoses (see Sadovnick et al. [1994] for more details).

Data Analyses

Morbidity risks for first-degree relatives (parents, siblings, and children) of index cases to also develop a mood disorder were calculated using the maximum likelihood approach, as described by Risch [1983]. This method assumes an age-of-onset distribution for relatives of index cases based on an "observed" age-of-onset

distribution, in the absence of accurate age-of-onset information for the relatives. In the present study, the age-of-onset distribution for mood disorders was based on data from the MDS Genetic Database [Sadovnick et al., 1994].

Age-of-onset of minor/intermittent depression or double depression for each index case was determined from the psychiatric consultation data. "Age-of-onset" was defined as the age at which the individual first had impairment associated with mood disorder symptoms [Egeland et al., 1987] or first sought medical treatment, if the former criterion was unclear (see Sadovnick et al. [1994] for more details).

The onset of unipolar depressive disorder (single depression or recurrent depression) is uncommon before age 10 years [Lewinsohn et al., 1986]. Up to 20% of individuals with bipolar depressive disorder have been reported to show evidence of illness during adolescence, although no mania was found below age 13 [Loranger and Levine, 1978]. A study [Bland et al., 1988] from a community sample of treated and untreated individuals, the results of which may be confounded by recall bias for the timing of the first symptom, found that mania is rare before age 10, and although major depressive episodes may occur before age 10, this is also rare. It was therefore decided to include only children age 10 years and over in calculating morbidity risks.

In calculating morbidity risks, relatives of index cases whose age at present (or at death) could not be estimated with a high degree of accuracy had to be excluded from analysis, even if that individual was known to have had a mood disorder. This was a rare occurrence.

Morbidity risks are presented ± SE for a better understanding of the position of the estimate used; 95% confidence intervals are twice the SE. Morbidity risks were compared using the likelihood ratio test [Risch, 1983], with differences significant at the 5% level.

RESULTS

Index Cases

A total of 146 consecutive unrelated index cases (95 females, 50 males) were identified with a diagnosis of minor/intermittent depression (N = 71, minor depression = 57, intermittent depression = 14) or double depression (N = 75). Sufficient data (sex, age at present or at death, knowledge about presence/absence of mood disorder symptoms, and ability to complete FHRDC questionnaires) were available on a total of 768 first-degree relatives of the index cases with minor/intermittent depression (N = 358) or double depression (N = 409). Table II describes the study group in more detail. It must be remembered that these data represent a subgroup of the entire MDS Genetic Database. Different totals may be found if comparing numbers presented in this paper with those in out previous paper [Sadovnick et al., 1994].

Morbidity Risks

Morbidity risk are presented in tabular form (Table III) as well as in the format of a genetic pedigree for easy reference (see Figs. 1–4). The data are presented according to the sex of the index case and for the following relationships to the index case: mother, father, sister, brother, and children (sons and daughters are combined because of the relatively low numbers). Comparisons of morbidity risks were made for various categories of relatives, according to the sex and diagnosis of the index case.

Minor/intermittent depression. Morbidity risks for first-degree relatives of female and male index cases with a diagnosis of "minor/intermittent depression" are presented in Table III and Figures 1a and b. No significant differences were found in the morbidity risks for mood disorders among first-degree relatives of these index cases.

Double depression. Female relatives (mothers, sisters) of female index cases had significantly higher rates of mood disorders compared with other categories of relatives. Female index cases had significantly more mothers than fathers ($G^2 = 7.77$; $P < 0.01$) and significantly more sisters than brothers ($G^2 = 4.04$; $P < 0.05$) who were affected with mood disorders (see Figs. 2a, b).

Major depression vs. minor/intermittent depression. Morbidity risks for first-degree relatives of index cases with major depression (single depression, recurrent depression) have been presented in detail elsewhere [Sadovnick et al., 1994]. No significant differences were found when these risks were compared with those for first-degree relatives of index cases with minor/intermittent depression (see Figs. 3a, b and 4a, b).

Major depression vs. double depression. Morbidity risks for first-degree relatives of index cases with major depression (single depression, recurrent depression) have been presented in detail elsewhere [Sadovnick et al., 1994]. No significant differences were found when these risks were compared with those for first-degree relatives of index cases with double depression.

Minor/intermittent depression vs. double depression. No significant differences were found when

TABLE II. Study Population

Diagnosis in index case	Index cases			Total number of first-degree relatives
	Female	Male	Total	
Minor/intermittent depression	46	25	71	358
Major depression[a]	279	160	439	2,656
Single depression	74	65	139	837
Recurrent depression	205	95	300	1,819
Double depression	50	25	75	409

[a]Sadovnick et al. [1994] for more details.

TABLE III. Comparison of Morbidity Risks for First-Degree Relatives of Index Cases With Minor Depression, Double Depression, and Major (Single or Recurrent) Depression

	Morbidity risk (%) ± SE index case diagnoses			
			Major depression[a]	
	Minor/intermittent depression	Double depression	Single depression	Recurrent depression
Relatives of female index cases				
Mothers	14.5% (5.5)	18.9 (5.7)	16.5% (4.6)	6.3% (1.8)
Fathers		2.2% (2.2)	6.0% (2.9)	2.1% (1.1)
Sisters	11.6% (5.6)	13.2% (5.1)	7.8% (3.4)	9.4% (2.0)
Brothers		2.3% (2.3)	5.5% (2.7)	1.7% (0.9)
Children	20.1% (10.9)	14.2% (9.6)		9.4% (2.8)
Relatives of male index cases				
Mothers	8.9% (6.0)	16.5% (7.6)	6.6% (3.2)	16.1% (4.0)
Fathers	4.9% (4.8)	12.7% (6.9)	1.7% (1.7)	3.5% (2.0)
Sisters	15.0% (10.0)		17.2% (5.9)	8.3% (2.8)
Brothers	4.9% (4.8)			5.7% (2.5)
Children		10.1% (9.9)		4.9% (3.4)

[a]See Sadovnick et al. [1994] for more details.

morbid risks for mood disorders among first-degree relatives were compared with index cases with minor/intermittent depression and double depression.

DISCUSSION

Using a genetic methodology of comparing morbidity risks for mood disorders among first-degree relatives of index cases with minor/intermittent depression or double depression, this paper explores the relationship among the diagnostic categories of minor/intermittent depression, major depression, and double depression. The results show no significant differences in morbidity risk calculations to first-degree relatives of index cases with one of these three diagnoses.

Whether minor/intermittent depression, major depression, and double depression lie in a continuum or are distinct clinical entities is an important research and clinical question that has yet to be resolved. Minor/intermittent depression has had many different labels, including neurotic depression, characterologic depression, depressive personality, chronic dysphoria, and the more recent DSM III-R category of dysthymic disorder. The objective operational criteria of RDC minor/intermittent depression and DSM III-R dysthymic disorder are a theoretical and shun hypotheses on the etiology of these disorders.

The results from this study are consistent with biological treatment and familial research studies suggesting more similarities than differences between minor/intermittent and major depression, as will be discussed below.

Howland and Thase [1991] thoroughly reviewed the biological studies comparing DSM III-R dysthymic disorder and major depression. In their review, they emphasized that long-term chronic RDC minor/intermittent depression is quite similar to the newer DSM III-R category of dysthymia. Sleep studies suggest more similarities than differences between dysthymic disorder and major depression. Reduced REM latency is the most consistent neurophysiological abnormality noted in patients with mood disorders, and has been considered a "biological marker" in depression [Kupfer and Ehlers, 1989]. Sleep studies where reduced REM latency was examined in patients with dysthymic disorder and major depressive disorder showed more similarities than differences between groups [Akiskal et al., 1980; Haurl and Satela, 1984; Cluydts et al., 1989]. Al-

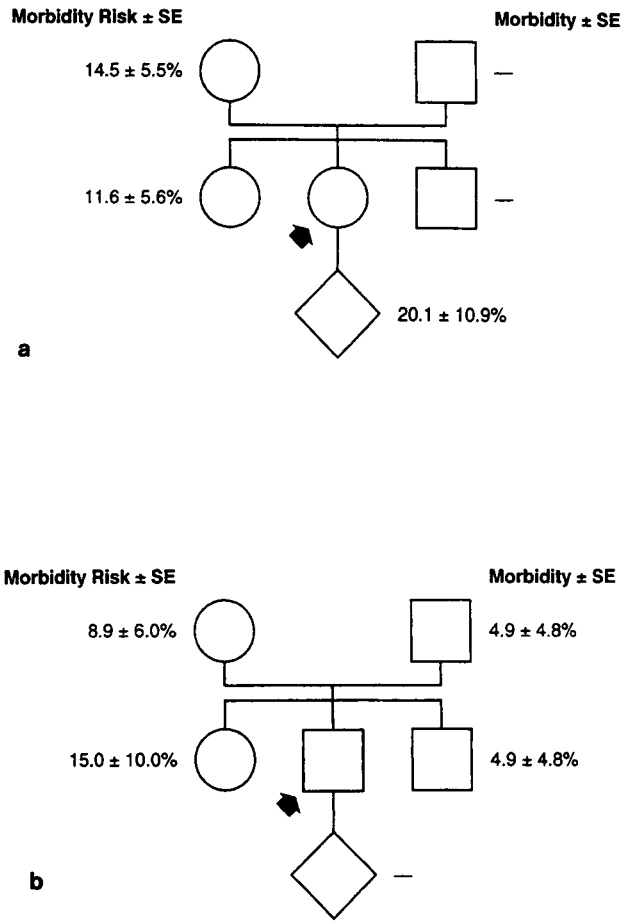

Fig. 1. Morbidity risks for mood disorder in first-degree relatives of index cases with minor/intermittent depression. **a:** Female index cases. **b:** Male index cases.

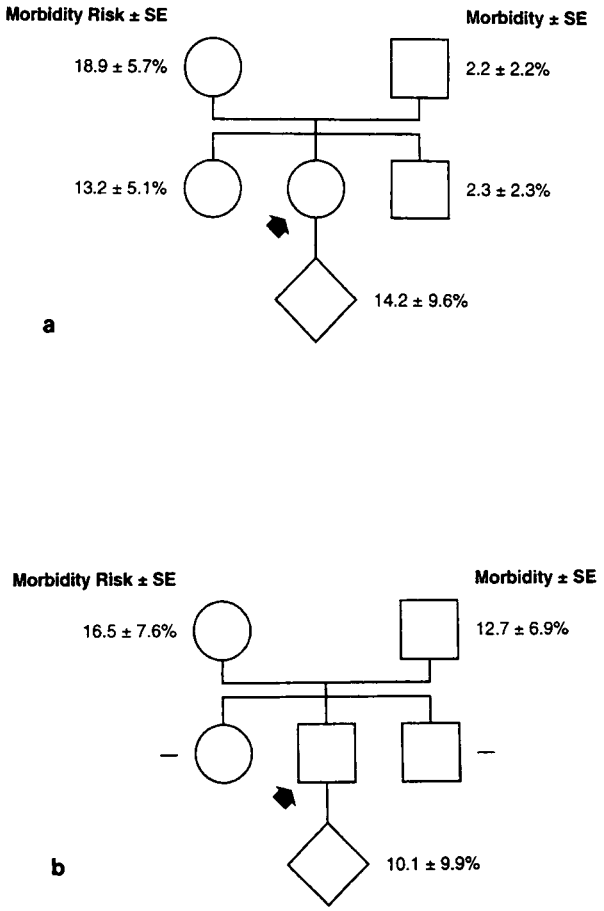

Fig. 2. Morbidity risks for mood disorder in first-degree relatives of index cases with double depression. **a:** Female index cases. **b:** Male index cases.

though sample sizes have been small and not consistently replicated [Gupta and Moldofsky, 1986; Palva et al., 1986], the reports (reviewed in detail by Howland and Thase [1991]) suggest the presence of this "biological marker" (i.e., reduced REM latency) not only in major depression but also in dysthymic disorder.

While not devoid of controversy, the dexamethasone suppression test (DST) has shown abnormalities (DST nonsuppression) in a sizable minority of major depressive patients, particularly in those with "melancholic" features. Studies comparing DST results in individuals with minor/intermittent and major depression show differences between the two groups in the majority of these studies [Nelson et al., 1984; Poirier et al., 1987; Henry et al., 1987; Ravindran et al., 1994], indicating a far higher percentage of DST nonsuppression in major depression compared with minor/intermittent depression. These observations are consistent with recent work suggesting that DST nonsuppression is a "state"-dependent phenomenon based on severity of illness and compatible with the concept of a continuum between the "milder" illness of dysthymic disorder and the more severe disorder of major depression.

A number of recent antidepressant treatment trials have shown more similarities than differences between dysthymia and major depression. Specifically, dysthymic patients often have an excellent response to antidepressant chemotherapy with tricyclic antidepressants and monoamine oxidase (MAO) inhibitors, as reviewed by Howland [1991]. More recent work has suggested that the serotonin reuptake inhibitor fluoxetine [Rosenthal et al., 1992; Ravindran et al., 1994] is also effective in treating both dysthymia and major depression.

Family studies have shown an increased risk of mood disorders in relatives of dysthymic patients compared with controls. For example, Klein et al. [1988b] reported that 84% of first-degree relatives of dysthymic patients had mood disorders, compared with 57% of controls although, to the best of our knowledge, no study has compared these risks with those for relatives of patients with major and double depression. A recent Canadian study found that 74% of first-degree relatives of patients with RDC minor/intermittent depression had depression [Ravindran et al., 1993]. These findings are consistent with our data, which suggest that familial risks for mood disorders are no higher (or lower) for relatives of dysthymic patients than for relatives of patients with major depression.

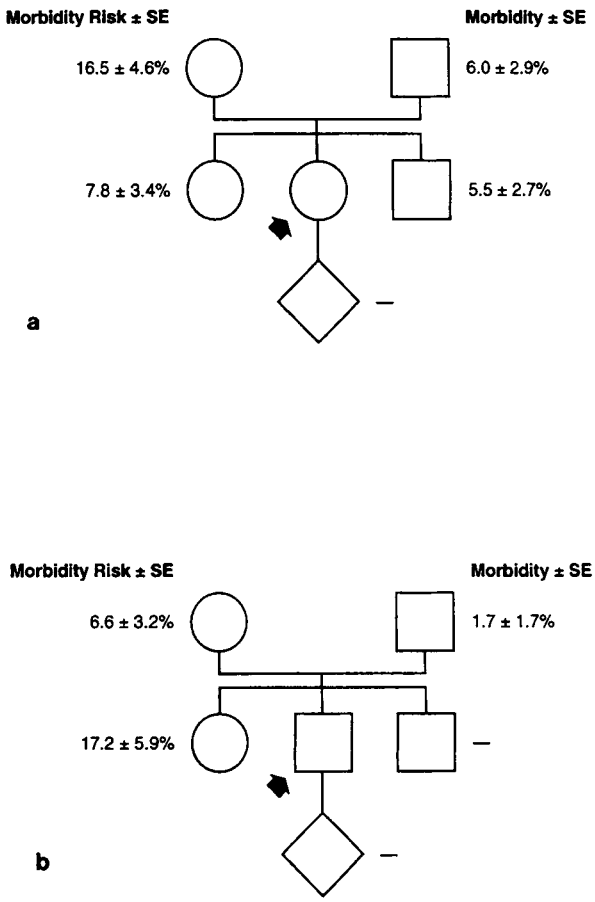

Fig. 3. Morbidity risks for mood disorder in first-degree relatives of index cases with single depression. **a:** Female index cases. **b:** Male index cases.

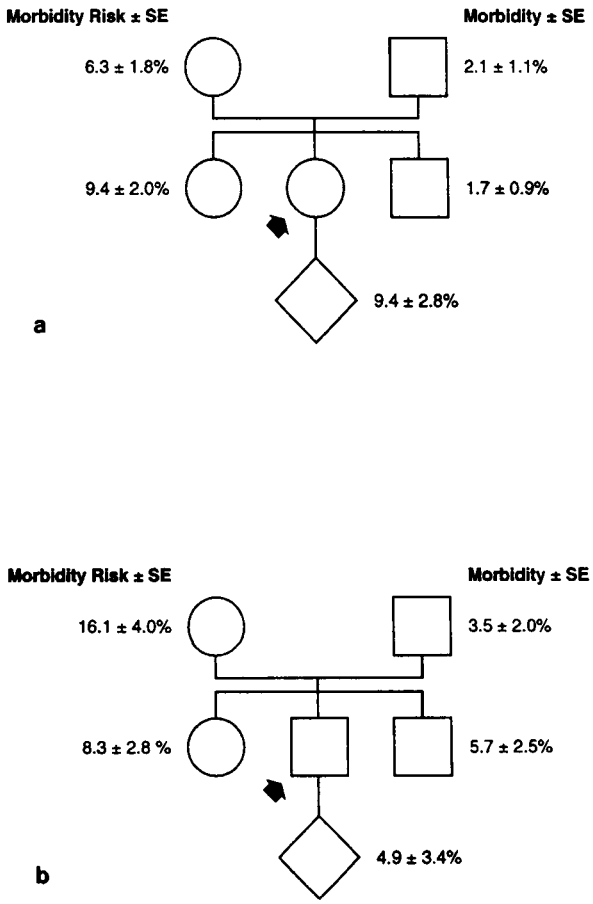

Fig. 4. Morbidity risks for mood disorder in first-degree relatives of index cases with recurrent depression. **a:** Female index cases. **b:** Male index cases.

Our findings are limited by some specific methodological flaws which were largely unavoidable. First, there are diagnostic differences between the DSM III-R concept of dysthymic disorder and the RDC category of minor/intermittent depression as discussed by others [Akiskal and Weise, 1992; Kocsis and Frances, 1987]. We emphasize here that our data are for the RDC categories of minor/intermittent depression and not dysthymic disorder. However, we do believe that the RDC categories in our study are quite similar to the DSM III-R diagnoses of dysthymia and major depression. Nevertheless, the data can only be presented here for RDC categories. Second, we were methodologically unable to directly assess all relatives of index cases. However, our rationale for this approach and its reliability has been presented in detail in a previously published paper [Sadovnick et al., 1994], and has been used in other published studies [Hirst et al., 1994; Weissman et al., 1986].

In summary, our data examined the relationship between minor/intermittent depression, major depression, and double depression. From the point of view of morbid risks for first-degree relatives to develop mood disorders, these three categories are not significantly different.

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